Depression: a major, unrecognized risk factor for osteoporosis?

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Existing studies of the relationship between depression and osteoporosis have been heterogeneous in their design and use of diagnostic instruments for depression, which might have contributed to the different results on the comorbidity of these two conditions. Nevertheless, these studies reveal a strong association between depression and osteoporosis. Endocrine factors such as depression-induced hypersecretion of corticotropin-releasing hormone and hypercortisolism, hypogonadism, growth hormone deficiency and increased concentration of circulating interleukin 6, might play a crucial role in the bone loss observed in subjects suffering from major depression.

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Depression is a common disorder affecting 5–9% of women and 1–2% of men[1]. This disorder carries a considerable risk of morbidity and is associated with a two–threefold increase in all-cause, non-suicide-related mortality, especially in men[2]. Hypercortisolism, a frequent finding in depressed patients (for a review see Ref. 3), might contribute to some of the somatic consequences of depression, including bone loss and alterations in body composition[4–8].

Osteoporosis is a condition characterized by bone fragility and increased risk of bone fracture[9]. Prevention of this common disorder should be reserved for subjects at risk; however, there is debate regarding which risk factors warrant further evaluation by measurements of bone mineral density (BMD). Evidence suggests that the diagnosis of osteoporosis should be considered when one or more of the accepted risk factors are present (personal or family history of previous fracture, thinness or current smoking)[10]. Therefore, the identification of unrecognized risk factors for osteoporosis is central to the diagnosis of osteoporosis and is not only of scientific interest, but also has considerable clinical consequences.

Low BMD is more frequent in depressed subjects than in the general population[11–13]. Because low BMD is one of the most important risk factors for osteoporotic fracture[14], these studies[11–13] suggest that depression might be a significant, but ignored, risk factor for osteoporosis. This review summarizes published evidence of depression as a risk factor for osteoporosis and balances the relevance of depression against currently established risk factors for this condition. Endocrine factors potentially responsible for the bone loss observed in subjects with depression, such as hypercortisolism, hypogonadism and growth hormone (GH) deficiency, are discussed further.

Depression and osteoporosis

Depression, BMD and fractures

A search was conducted on 'osteoporosis and depression' using MEDLINE, Biosis, Previews, Social Sciences Abstracts, SocialSciSearch, Ageline, Embase, Pascal, SciSearch, Psych Info, and Health & Wellness. These databases were searched for the total time for which data were available and the results are summarized in Table 1 and in Fig. 1.

In the first study, trabecular bone density, assessed by single-energy quantitative computed tomography (CT) at the lumbar spine, was ~15% lower in 80 men and women older than 40 years suffering from major depression [as defined by Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria] compared with 57 non-depressed men and women[12]. Factors with a potential to influence bone loss, such as smoking, lifetime history of excessive or inadequate physical exercise or history of estrogen treatment did not affect the regression model, suggesting that depression *per se* had an effect on bone mass. However, age at onset and total duration of depression did not reveal a significant influence on bone mass. As pointed out in a subsequent letter[15], female and male comparison subjects had similar lumbar BMDs, which raises the question of how representative of the general population the comparison group was.

A follow-up study conducted in 18 depressed men and women and 21 comparison subjects from the original cohort indicated that bone loss over a period of at least 24 months was 10–15% greater in depressed subjects[13]. Interestingly, bone loss was also about 6% greater in depressed men than in depressed women. The few subjects included in this study limited its statistical power, and made the matching of controls by sex, age and body mass index (BMI) uncertain. Caution should also be exercised in interpreting this follow-up study, which included only half of the subjects originally studied.

In the third study, BMD was measured by dual-energy X-ray absorptiometry (DEXA) at the spine, hip and radius in 22 pre- and two postmenopausal women with previous or current major depression[11]. The 24 controls were matched by age, menopausal status, race and BMI. BMD was 6% lower at the spine and 14% lower at the hip in depressed women than in controls. In ten of the depressed premenopausal women, BMD was at least 2 SD below the young normal mean value, which represents severe osteopenia[9]. By

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Table 1. Summary of reports on depression and osteoporosis[a]

Subjects (mean age)	Measurements	Study design/setting	Evaluation of depression	Findings	Refs
27 depressed men (58 years) 53 depressed women (62 years) 30 non-depressed men (63 years) 58 non-depressed women (58 years)	Spine BMD by single-energy CT	Cross-sectional	DSM-III R	15% lower spine BMD in depressed subjects	12 (study 1)
10 depressed men (57 years) 8 depressed women (61 years) 14 non-depressed men (65 years) 7 non-depressed women (63 years)	Same as study 1	Longitudinal over at least 24 months Follow up on study 1	Same as study 1	10–15% greater bone loss over at least 24 months in depressed subjects 6% greater bone loss in depressed men than in in depressed women	13
24 depressed women (41 years) 24 control women (41 years)	BMD by DEXA at the spine, hip and radius Biochemical markers of bone turnover Cortisol, PTH, vitamin D, IGF-1	Cross-sectional	DSM-III R	6–14% lower BMD in depressed women at the spine and hip	11
467 depressed women (75 years) 6949 controls (73 years)	BMD by DEXA at the spine and hip Falls and fractures	Prospective cohort over 3.7 years	Geriatric Depression Scale	Greater incidence of falls (OR 1.6) and fracture (OR 2.3), but no differences in BMD between depressed and non-depressed women	16
33 women (44 years) 35 men (36 years) with various mental disorders 21 depressed subjects	BMD by DPA at the spine and hip Testosterone (in men), estradiol (in women) prolactin, cortisol	Observational study of hospitalized patients	DSM-III R	Low BMD in depressed subjects, especially depressed men Inverse correlation between plasma cortisol and BMD	20
102 women randomly selected (58 years)	BMD at the spine and hip by DEXA	Cross-sectional Population-based	Beck Depression Inventory Hopkins Symptom Checklist-90	25–35% higher scores of depressive symptoms and depression in women with osteoporosis	21
121 healthy postmenopausal women (63 years)	BMD at the spine and hip by DEXA	Cross-sectional study of screened patients at a clinic for osteoporosis	General Health Questionnaire	No association between depressive symptoms and BMD	23

[a]Abbreviations: BMD, bone mineral density; CT, computed tomography; DEXA, dual-energy X-ray absorptiometry; DPA, dual-photon absorptiometry; IGF-1, insulin-like growth factor 1; OR, odds ratio; PTH, parathyroid hormone.

contrast, no premenopausal woman in the control group had a deficit of similar magnitude. It is also of interest that, unlike other forms of osteoporosis, including postmenopausal osteoporosis, bone loss was greater at the hip than the spine in women suffering from depression. Because the risk of fracture increases by a factor of 1.5–3 for each SD reduction in BMD (Refs 15,16), a substantial lifetime risk of osteoporotic fractures related to depression was already established before menopause. Markers of bone turnover, serum osteocalcin, urinary deoxypyridinoline crosslinks and urinary N-telopeptide crosslinks of type I collagen, were about 15–30% lower in depressed women than in controls, indicating reduced bone turnover in depressed patients. Although still within the normal range in many of the patients, urinary free cortisol excretion was ~40% higher in depressed women than in controls.

In a multicenter, prospective cohort study of 7414 elderly women, the association between depression, BMD, falls and risk of fracture was examined[16]. Unlike the previously described studies, this study used the Geriatric Depression Score, a 15-item validated checklist of symptoms designed to detect depression in the elderly. BMD was measured by DEXA at the spine and hip. Incident vertebral fractures were documented by follow-up spine X-rays. Self-reported falls were ascertained during the follow-up visits. The prevalence of depression was 6%, consistent with reports by others[1]. Depressed women were more likely to fall (70% versus 59%), and had a greater incidence of vertebral (11% versus 5%) and non-vertebral (28% versus 21%) fractures compared with controls. In spite of this, BMD was similar in women with and without depression, which might imply that there is an association between depression and fractures, rather than between depression and osteoporosis *per se*. However, in data-driven analyses, the authors also found that, in a subgroup of the original cohort – the tertile of subjects with the highest BMI (>27.6 kg m^{-2}) – women with depression had a 3–5% lower bone

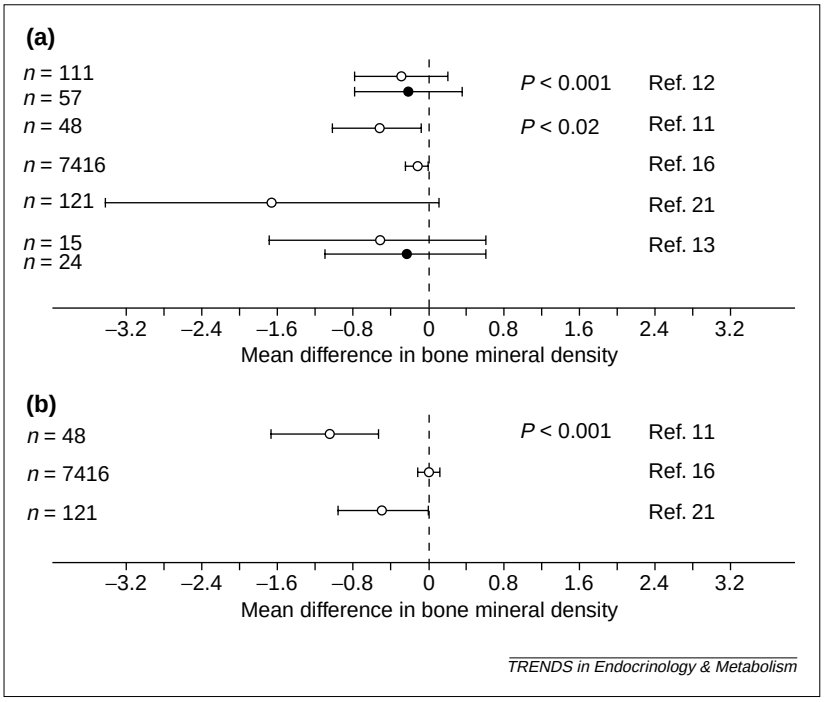

Fig. 1. Studies comparing bone mineral density in subjects with and without depression: 95% confidence intervals for the mean difference in bone mineral density between depressed and non-depressed subjects at (a) the spine and (b) the hip computed from all the published studies, chronologically listed, that reported mean ± SD absolute values for bone mineral density. Filled circles, men; open circles, women.

mass than did those without depression. Because low BMI and thinness, rather than increased body weight, is a risk factor for osteoporosis[17], the physiological relevance of this finding is unclear. Correction for a greater propensity to fall in depressed women did not fully explain the increased risk of fracture seen in women who also had depression. Adjustment for use of antidepressants, sedatives and hypnotics did not influence the association between depression and fractures. To explain these findings, the authors proposed that falls by depressed women might be related to non-specific factors, such as poor adjustment to old age, which suggests that the association between depression and low BMD might be limited to younger women and/or to women with more severe, long-lasting depression. Finally, it should be noted that degenerative bone changes make BMD measurements less reliable in the elderly[18,19], which might, in part, explain the insignificant association between BMD and fracture seen in this population. With all the limitations noted above, this study underscores the importance of depression as a risk factor for osteoporotic fractures.

In a study of 35 men and 33 women consecutively hospitalized for mental disorders, BMD was measured by dual-photon densitometry at the spine and hip[20]. The patients suffered from depression, schizophrenia, mania, schizoaffective disorder or adjustment disorders. Patients with depression or schizophrenia had significantly lower BMD than did age- and sex-matched controls and, in general, bone loss was more severe in depressed men than in depressed women. A negative association between serum cortisol levels and BMD was observed in depressed subjects of both sexes. In men, there was a positive correlation between BMD and testosterone levels, whereas in women, estradiol levels did not correlate with BMD.

The relationship between osteoporosis and indices of well-being or psychopathology was evaluated in a community sample of 102 Portuguese ambulatory middle-aged women[21]. Depressive symptoms were evaluated by the Beck Depression Inventory and BMD was measured by DEXA at the spine and hip. The prevalence of osteoporosis in this sample was 47%, which corresponds to reports from epidemiological studies[22]. Depression was significantly more common in women with osteoporosis than in women without it (77% versus 54%), corresponding to an odds ratio (OR) of depression in women with osteoporosis of 2.9 (95% confidence interval, 1.0 to 7.6); women with osteoporosis had ~25–35% higher depressive scores than did women with normal bone mass. The association between depression and osteoporosis was independent of other risk factors for osteoporosis, such as age or BMI. No differences were found in the general well-being scores, suggesting that depression was not a consequence of pain or physical distress in these asymptomatic women with a diagnosis of osteoporosis based on BMD determination.

Depressive symptomatology was assessed by the General Health Questionnaire in 121 postmenopausal women who spontaneously attended a screening visit for osteoporosis[23]. BMD was measured by DEXA at the spine and hip. Importantly, this study did not find an association between depressive symptoms or a depressive trait and low BMD, suggesting that only fully developed depression is a risk factor for osteoporosis.

Psychotropic medications, falls and fractures

Use of antidepressants, sedatives and hypnotics is associated with a greater incidence of falls and fractures, especially in the elderly[24]. These medications can increase the risk of falling by various mechanisms, such as by inducing orthostatic hypotension and syncope, dizziness, vertigo, blurred vision, ataxia or somnolence. The association between hip fractures, falls and use of two commonly prescribed classes of antidepressants – tricyclic antidepressants (TCAs) or selective serotonin-reuptake inhibitors (SSRIs) – was investigated in a case-control study[25]. Each of the 8239 elderly men and women treated in a hospital setting for hip fracture within a 12 month period was matched by age and gender to five controls. Hospital records determined comorbidity and risk of falls during the three years preceding the hip fracture. Most of the cases were women (78%) and a large proportion was older than 85 years (40%). Depression was approximately three times more common in patients

with hip fracture than in controls (14.9% versus 5.7%). Of the patients with hip fracture, 6.6% had been exposed to SSRIs, 2.6% to secondary TCAs and 9.0% to tertiary TCAs. After adjustment for confounding variables, the OR for hip fracture was 1.5 in patients exposed to tertiary TCAs and 2.4 in patients exposed to SSRIs. Consistently, current users of antidepressants had a higher risk than did former users and there was no relation between dose of antidepressants and risk of hip fracture. Because BMD was not measured in this study, it was not possible to establish whether the increased risk of fracture seen in depressed subjects reflected an underlying association between low BMD and depression. In addition, the study design did not allow for conclusions on causal relations, so the possibility remained that depression was, in part, the result of a debilitating fracture.

In another case-control study of elderly residents of a long-term facility, the incidence of falls was correlated to general health and use of medications[26]. There was a significant association between the number of falls and the number of medications that the subjects were taking and, in general, this association related more to the prescribed drug than to the symptoms or to the disease that initially required prescription. In addition, the use of three or more drugs increased the risk of falling. Only depression and osteoarthritis were consistently associated with an increased risk of falling across the 12 therapeutic classes of drugs, which suggests an independent effect of these two medical conditions.

In addition to potentially impairing arousal and balance and thereby increasing the risk of falls, many of the drugs prescribed for depression have an effect on Ca^{2+} metabolism and, possibly, on BMD. However, it is unclear whether this effect contributes to the fractures resulting from drug-related falls. Lithium carbonate, a drug primarily used for bi- and unipolar affective disorders, potentiates the Ca^{2+}-induced inhibition of parathyroid hormone (PTH) secretion[27]. Use of this drug has been associated with secondary hyperparathyroidism[28,29]. In a small, cross-sectional study, BMD at the spine and hip, and plasma Ca^{2+} and PTH levels were normal in 23 patients (five men and 18 women) treated with lithium for various affective disorders over a period of 0.6–9.9 years[30]. Thyroid-stimulating hormone (TSH)-suppressive doses of thyroxine treatment have a negative effect on BMD (Ref. 31). Both thyroxine and triiodothyronine are sometimes used in doses sufficient to suppress TSH as adjunct treatment to antidepressive therapy in patients with major depression or rapid-cycling bipolar disorders, but little is known about the effect of this treatment on BMD. A small, cross-sectional study evaluated BMD in ten (nine pre- and one postmenopausal) women with bipolar disorder treated with thyroxine for at least 18 months[32] and found that the use of thyroxine was not associated with decreased BMD at any site.

Potential mechanisms of bone loss in depression

One mechanism by which depression might induce bone loss is hypercortisolism. Osteoporosis is a known consequence of hypercortisolism resulting from endogenous Cushing's syndrome and chronic steroid use. Bone loss in Cushing's syndrome seems to be primarily caused by decreased bone formation[33], and the contribution of increased bone resorption is unknown. Bone loss is more pronounced in trabecular than in cortical bone and frequently leads to fractures[34]. The degree of bone loss correlates with the severity and duration of this condition rather than with the underlying cause[33]. This includes the factitious and drug-related forms[35]. Bone mass is only partially regained once the disease is cured, and the process can take many years[33].

Hypercortisolism, a well-known biological correlate of depression, might be the consequence of dysregulation of the corticotropin-releasing hormone (CRH) system and the hypothalamic–pituitary–adrenocortical axis[8] (Fig. 2). CRH hypersecretion and hypercortisolism in turn lead to inhibition of the reproductive axis and hypogonadism. Hypogonadism is an established risk factor for bone loss in both sexes[36]. In addition, CRH hypersecretion and hypercortisolism decrease the activity of the GH–insulin-like growth factor 1 axis, an important enhancer of bone formation[8]. In depression, dysregulation of several inflammatory mediators has been reported, including interleukin 6 (IL-6), which might be involved in some of the other medical consequences of major depression, such as cardiovascular disease and insulin resistance[37,38]. IL-6, a major mediator of bone resorption, is raised in depressed subjects, especially at an older age[39]. Increased sympathetic activity, often seen in depressed subjects[40], also concurs to increase IL-6 secretion.

Recently, it was reported that leptin, a hormone secreted by white adipose tissue, inhibits bone formation through a central mechanism involving a hypothalamic relay[41]. Intracerebroventricular administration of leptin to leptin-deficient *ob/ob* mice, a strain characterized by abnormally increased bone mass, in addition to causing marked inhibition of food intake, increased energy expenditure and weight loss, also induces bone loss. This effect is centrally mediated at the level of the hypothalamus, and does not involve a direct effect of circulating leptin on bone cells, because leptin receptors are not present on osteoblasts or other bone cells. Because the secretion of leptin is increased at night in depressed subjects[42], we hypothesize that an additional mechanism of bone loss in major depression is central inhibition of bone formation by leptin. Interestingly, the phenotype of the *ob/ob* mice includes hypercortisolism and hypogonadism, two features also common in depressed subjects. Finally, both major depression and osteoporosis are probably associated with multiple genes. Genes involved in the regulation of phospholipids might be associated with

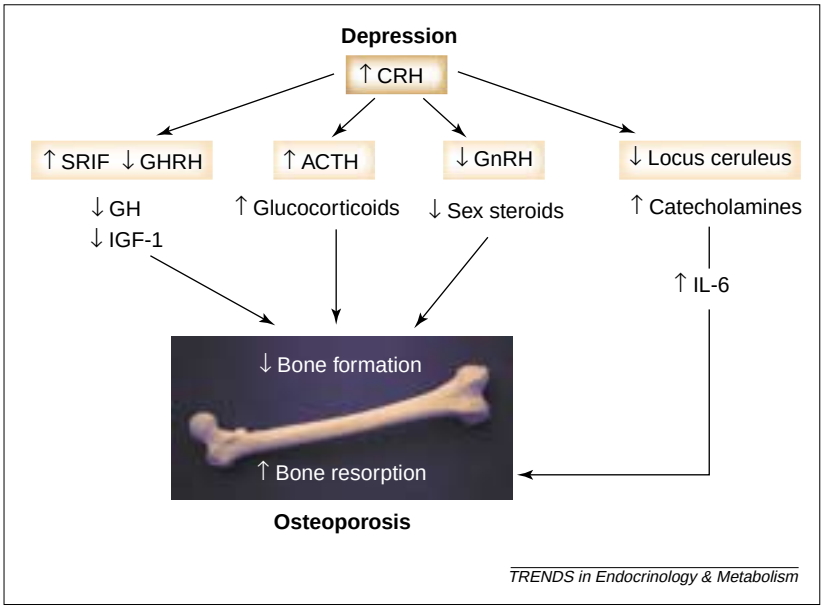

Fig. 2. The proposed endocrine mechanisms contributing to bone loss in subjects suffering from depression. Major depression is associated with increased secretion of CRH and glucocorticoids along the hypothalamic–pituitary–adrenal axis[6,8]. CRH, in turn, inhibits the gonadal axis affecting the hypothalamic release of GnRH and inhibits the GH axis via stimulation of somatostatin and inhibition of GHRH (Ref. 8). Increased secretion of cortisol, decreased secretion of GH and IGF-1, and decreased secretion of sex steroids result in decreased bone formation and increased bone resorption[8]. High levels of catecholamines stimulate the production of IL-6, a potent bone resorption factor[37]. The concurrent increased bone formation and decreased bone resorption leads to a net bone loss. Abbreviations: ACTH, adrenocorticotropin; CRH, corticotropin-releasing hormone; GH, growth hormone; GHRH, GH-releasing hormone; GnRH, gonadotropin-releasing hormone; IGF-1, insulin-like growth factor 1; IL-6, interleukin 6; SRIF, somatostatin. Inset photo courtesy of PhotoDisc Inc.

both conditions[43]; whether depression and osteoporosis share a common genetic predisposition, mediated by a common genetic set-up, remains to be determined.

So far, the relation between depression and osteoporosis has been discussed based upon the hypothesis that depression induces bone loss, via all the potential biological mechanisms discussed above. Osteoporosis can be a silent disease and, as such, might go undiagnosed for a long time, until pathological fractures ensue. Several of the studies reviewed reported upon subjects suffering from major depression in whom bone loss was asymptomatic and undiagnosed. It is unlikely that a largely asymptomatic condition (osteoporosis), of which the subject is not aware, would induce depressive symptoms. However, bone loss does eventually cause fractures, which, especially if at the hip site, are very serious and disabling conditions – quality of life is profoundly threatened by falls and hip fractures among elderly women[44]. In this scenario, it is conceivable that clinical osteoporosis, especially if it causes pain and physical disability, might induce reactive depressive symptoms. Whether such depressive symptoms are followed by changes in cortisol and other hormones remains to be determined. In summary, the relation between depression and osteoporosis, similarly to other clinical situations such as stroke, rheumatoid arthritis or other debilitating conditions in which depression coexists with a medical condition, should be seen as a bidirectional one, with the two conditions influencing each other in a vicious circle.

Conclusions

The studies outlined found a consistent association between depression and osteoporosis, suggesting that depression is a substantial, yet previously unrecognized, risk factor for osteoporosis, similar to other well-established risk factors, such as low BMI, smoking or family history of osteoporosis[45]. However, to date, the nature of the relation between these two conditions is only partly elucidated. It is therefore important to note some of the limitations of the literature reviewed. First, most studies were cross-sectional and were, by design, only able to indicate associations rather than causal links. Furthermore, different diagnostic systems were used to diagnose and estimate the severity of depression. These differences might have contributed to the range of prevalence of depression reported in subjects affected by osteoporosis. In several studies of bone loss, actively depressed subjects were pooled with subjects who only carried a historical diagnosis of depression. It is a problem that we do not know whether the impact on bone loss of current depression is equivalent to past history of depression. Retrospective evaluation of depression has limited reliability when it is based solely upon subject recollection[12,13]. In addition, many studies were small with heterogeneous patients. Importantly, when the diagnosis of major depression was used as the 'threshold' for severity of depression – a far more severe condition than depressive symptomatology – most studies found a clear association between depression and osteoporosis.

Finally, any review of the literature of this kind might have an inherent selective publication bias because studies that fail to prove the original hypothesis, either as a result of lack of statistical power or because the hypothesis proved to be untrue, are three or more times less likely to be published than are positive studies, a phenomenon known as the 'file drawer problem'[46]. Therefore, there might be unpublished studies of which we are unaware that failed to find an association between depression and osteoporosis, or that proved that there is no association between these two conditions. To reduce the possibility of such bias, some advocate the institution of a registry listing all the clinical studies that are started on a given research topic.

Within these limitations, the studies discussed raise questions that should be addressed in the future. The existence of a causal link between depression and osteoporosis, and whether bone loss only occurs when a patient is actively depressed, should be determined. In addition, it should be established whether successful treatment of depression and/or use of antidepressants *per se* have any impact on bone turnover. The prevalence of

osteoporosis in depression should be further investigated. It should be established whether there is a subgroup of depressed subjects at particular risk of osteoporosis who might be candidates for osteoporosis treatment. More research is needed to understand the putative role of depression in male osteoporosis. This condition is poorly understood, relatively neglected until very recently and labeled as 'idiopathic' in approximately one-third of subjects[47,48]. At a mechanistic level, it is crucial to understand the specific role of the endocrine and paracrine factors responsible for bone loss in depression and the relative contribution to bone loss of decreased bone formation and increased bone resorption.

Only prospective, long-term studies with sufficient statistical power will be able to answer these questions and allow insight into the pathogenesis of bone loss in depression. In conclusion, the clinical evaluation of subjects with idiopathic bone loss, especially premenopausal women and young or middle-aged men, should also include an assessment of depression. Conversely, a history of non-traumatic fractures in a depressed subject should alert the physician to the possibility of undiagnosed osteoporosis.

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